

Q3 Claim 45 (Amended) The method of claim 69 wherein the third intracellular loop of the receptor of step (a) comprises the following sequence:

X1BBHyX2

Wherein X1 is an amino acid; B is a basic amino acid; Hy is a hydrophobic amino acid; and X2 is an amino acid.

Q4 Claim 52 (Amended) The method of claim 69 wherein the second intracellular loop of the receptor of step (b) comprises the following sequence:

XRY

wherein X can be any amino acid other than aspartic acid; R is arginine; and Y is tyrosine.

Claim 53 (Amended) The method of claim 70 wherein the third intracellular loop of the receptor of step (a) comprises the following sequence:

X1BBHyX2

wherein X1 is an amino acid; B is a basic amino acid; Hy is a hydrophobic amino acid; and X2 is an amino acid.

Q5 Claim 60 (Amended) The method of claim 70 wherein the second intracellular loop of the receptor of step (a) comprises the following sequence:

XRY

wherein X can be any amino acid other than aspartic acid; R is arginine; and Y is tyrosine.

Q6 Claim 63 (Amended) The method of claim 69 wherein said mammal of step (d) is a human.

Claim 64 (Amended) The method of claim 70 wherein said mammal of step (d) is a human.

Claim 65 (Amended) The method of claim 69 wherein said mammal of step (d) is a non-human.

Claim 66 (Amended) The method of claim 70 wherein said mammal of step (d) is a non-human.

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Claim 67 (Amended) The method of claim 69 wherein said physiological function is an abnormal physiological function.

Claim 68 (Amended) The method of claim 70 wherein said physiological function is an abnormal physiological function.

Please cancel claims 33 and 39 without prejudice.

Please add new claims 69-76 as follows.

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Claim 69 (New) A method for directly identifying a non-endogenous candidate compound as an agonist or an inverse agonist to an endogenous G protein coupled receptor (GPCR), wherein a location of expression of said receptor in a mammalian tissue source is known and said receptor has been correlated with at least one mammalian physiological function and wherein an endogenous ligand for said receptor has not been identified, said method comprising the steps of:

(a) subjecting said GPCR to constitutive receptor activation to create a constitutively activated GPCR;

(b) contacting the non-endogenous candidate compound with said constitutively activated GPCR;

(c) identifying said non-endogenous candidate compound as an inverse agonist or an agonist to said constitutively activated GPCR by measuring at least a 30% difference in a reporter signal induced by said contacted compound as compared with a reporter signal in the absence of said contacted compound.

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Claim 70 (New) A method for directly identifying a non-endogenous candidate compound as an agonist or an inverse agonist to an endogenous constitutively activated G protein coupled receptor (GPCR), wherein a location of expression of said receptor in a mammalian tissue source is known and said receptor has been correlated

with at least one mammalian physiological function and wherein an endogenous ligand for said receptor has not been identified, said method comprising the steps of:

(a) contacting the non-endogenous candidate compound with said constitutively activated GPCR;

(b) identifying said non-endogenous candidate compound as an inverse agonist or an agonist to said constitutively activated GPCR by measuring at least a 30% difference in a reporter signal induced by said contacted compound as compared with a reporter signal in the absence of said contacted compound.

Claim 71 (New) A compound directly identified by the method of claim 69.

Claim 72 (New) A compound directly identified by the method of claim 70.

Claim 73 (New) A pharmaceutical composition comprising the compound of claim 71.

Claim 74 (New) A pharmaceutical composition comprising the compound of claim 72.

Claim 75 (New) The method of any one of claims 69 or 70 wherein said location of expression of said receptor and said correlated physiological function are selected from the group of locations and correlated physiological functions consisting of groups 1-147 as follows:

1. gastrointestinal tract smooth muscle / motility of stomach and intestines;
2. gastrointestinal tract ganglionic nerve fibers / motility of stomach and intestines;
3. urinary tract smooth muscle / ureter function and urinary bladder function;
4. salivary gland / salivary secretion;
5. alpha cells of the pancreas / secretion of glucagons;
6. beta cells of the pancreas / secretion of insulin;
7. uterine smooth muscle / uterine contraction;
8. heart muscle / contractility of heart muscle;
9. vascular smooth muscle / contractility of smooth muscle;

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10. adipocytes / lipolysis;
 11. platelets / platelet aggregation in response to blood vessel injury;
 12. skeletal neuromuscular junction / skeletal muscle contractility;
 13. bronchial smooth muscle / respiration;
 14. nasal mucosal blood vessels / mucosa volume;
 15. trigone muscle of bladder and urethra / urinary outflow;
 16. chondrocytes / cartilage formation;
 17. ciliary body of the eye / aqueous humor production;
 18. thyroid / thyroid hormone secretion;
 19. mast cells / immediate hypersensitivity reactions;
 20. basophils / immediate hypersensitivity reactions;
 21. osteoblasts / bone remodeling;
 22. osteoclasts / bone remodeling;
 23. brain capillary endothelial cells / permeability of blood-brain barrier;
 24. T cells / immune response;
 25. B cells / immune response;
 26. kidney proximal tubular epithelial cells / organic acids exchange;
 27. neutrophils / immune response;
 28. eosinophils / immune response;
 29. monocytes / immune response;
 30. kidney late distal tubule / organic bases exchange;
 31. collecting duct principal cells / organic bases exchange;
 32. kidney granular juxtaglomerular cells / secretion of rennin;
 33. peripheral postganglionic adrenergic neurons / sympathetic function;
 34. hepatocytes / synthesis of cholesterol and lipoprotein;
 35. gastrointestinal parietal cells / secretion of stomach acid;
 36. gastrointestinal superficial epithelial cells / secretion of cytoprotective factors, mucus and bicarbonate;
 37. epidermal cells / skin maintenance;
 38. bone marrow stem cells / erythropoiesis production;
 39. angle structures of the eye / aqueous humor outflow;
 40. uveoscleral structures of eye / aqueous humor outflow;

41. suprachiasmatic nucleus / circadian rhythm;
42. baroreceptors / blood pressure;
43. basal ganglia / movement control;
44. periaqueductal grey and dorsal horn of spinal cord / nociception;
45. area postrema / vomiting;
46. thalamus / sensorimotor processing and arousal;
47. sensorimotor cerebral cortex / sensorimotor processing;
48. spinal cord motor neurons / motor function control;
49. dorsal root ganglion neurons / sensory information transmission;
50. oligodendrocytes / neuron myelin sheath production;
51. nucleus basalis / cognition and memory;
52. nucleus accumbens / addictive cravings;
53. lateral reticular formation of medulla / vomiting;
54. hypothalamic neurons containing growth hormone releasing factor (GHRH) / secretion of GHRH;
55. hypothalamic neurons containing somatostatin / secretion of somatostatin;
56. hypothalamic neurons containing thyrotropin-releasing hormone (TRH) / secretion of TRH;
57. hypothalamic neurons containing gonadotropin releasing hormone (GnRH) / secretion of GnRH;
58. hypothalamic neurons containing corticotropin releasing factor (CRF) / secretion of CRF;
59. anterior pituitary somatotropes / secretion of growth hormone;
60. anterior pituitary lactotropes / secretion of prolactin;
61. anterior pituitary gonadotropes / secretion of luteinizing hormone;
62. anterior pituitary gonadotropes / secretion of follicle stimulating hormone;
63. anterior pituitary corticotropes / secretion of adrenocorticotrophic hormone;
64. leydig cells of the testes / secretion of testosterone;
65. sertoli cells of the testes / spermatogenesis;
66. granulosa cells of the ovary / synthesis of estrogen;
67. theca cells of the ovary / synthesis of estrogen;
68. synovium / joint function;

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69. amygdala / modulation of emotion;
 70. pineal gland / regulation of circadian rhythm;
 71. nucleus of the solitary tract / cardiovascular regulation;
 72. caudal ventrolateral medulla / cardiovascular regulation;
 73. rostral ventrolateral medulla / vasopressor activity;
 74. parabrachial nucleus / taste aversion response and nociceptive response;
 75. entorhinal cortex / cognition;
 76. pyriform cortex / cognition;
 77. temporal cortex / memory acquisition;
 78. frontal cortex / regulation of emotional response and memory acquisition;
 79. parietal cortex / visual acuity, touch perception, and voluntary movement;
 80. occipital cortex / visual acuity;
 81. hippocampus / learning and memory;
 82. dentate gyrus / learning and memory;
 83. midbrain reticular formation / arousal;
 84. supraoptic nucleus of the hypothalamus / reproductive functions;
 85. magnocellular of the hypothalamus / modulation of stress, blood pressure and lactation;
 86. parvocellular neurons of the hypothalamus / metabolism;
 87. arcuate nucleus of the hypothalamus / release of pituitary hormones;
 88. trigeminal area / cerebral vessel dilation and blood pressure;
 89. cerebral blood vessels / cerebral vessel dilation;
 90. brain stem / breathing, heart rate, startle responses, sweating, blood pressure, digestion and body temperature;
 91. ventral lamina terminalis / blood pressure;
 92. vagus nerve / blood pressure and heart rate;
 93. nucleus of the solitary tract / blood pressure;
 94. adrenal medulla / catecholamine response to stress;
 95. adrenal cortex / stress-induced corticosterone release;
 96. locus coeruleus / arousal and response to stress;
 97. substantia nigra / control of body movement;
 98. ventral tegmental area / control of body movement;

99. olfactory bulb / odor perception;
100. median eminence of hypothalamus / pituitary function;
101. raphe nuclei / sleep and arousal;
102. habenula / sexual activity;
103. cerebellum / control of body movement;
104. posterior hypothalamus / intestinal motility and blood pressure;
105. dorsal medulla / blood pressure;
106. lateral hypothalamus / food intake and stomach acid secretion;
107. rostral hypothalamus / heart rate;
108. pontine-medullary reticular formation / respiration and heart rate;
109. medulla / respiration and heart rate;
110. mesencephalon / heart rate;
111. ventral hypothalamus / response to stress;
112. paraventricular nucleus of hypothalamus / response to stress;
113. preoptic area of hypothalamus / sexual activity;
114. mammillary region / food intake;
115. perifornical area of hypothalamus / food intake;
116. ventromedial hypothalamus / food intake;
117. pons/reticular formation / arousal and wakefulness;
118. septum / emotional control;
119. pedunclopontine tegmental nucleus / arousal;
120. astrocytes / neuronal metabolism;
121. microglia / response to neuronal injury;
122. choroid plexus / production of cerebrospinal fluid;
123. Schwann cells / myelination of peripheral nerves;
124. endoneurium / production of connective tissue nerve sheath;
125. lateral spinothalamic pathway / response to pain and temperature stimuli;
126. ventral spinothalamic pathway / touch sensation;
127. dorsal column-medial lemniscal pathway / touch sensation;
128. free nerve endings / response to pain and temperature;
129. hair follicle endings / touch sensation;
130. Krause's end-bulb / temperature sensation;